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(54) Title: NOVEL ANALGESIC AND IMMUNOMODULATORY CANNABINOIDS

(57) Abstract

Disclosed are novel compounds represented by the following structural formula: R–X–Y; and physiologically acceptable salts thereof. R is a tricyclic core of a cannabinoid or substituted cannabinoid. X is a covalent bond, $-CH_2-$ or $-CHR_1-$, wherein R_1 is a C1 to C3 substituted or unsubstituted alkyl group. Y is a heterocyclic ring, a substituted heterocyclic ring, a carbocyclic ring, a substituted carbocyclic ring, a fused bicyclic ring system, a substituted fused bicyclic ring system, a bridged bicyclic ring system, a substituted bridged bicyclic ring system, a bridged tricyclic ring system or a substituted bridged tricyclic ring system. Also disclosed is a method of stimulating a CB1 and/or CB2 receptor in a subject. The method comprises administering to the subject a therapeutically effective amount of R–X–Y.

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NOVEL ANALGESIC AND IMMUNOMODULATORY CANNABINOIDS

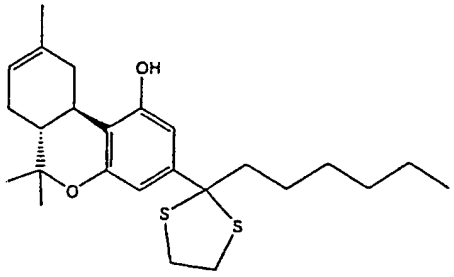
BACKGROUND OF THE INVENTION

Δ^8-Tetrahydrocannabinol, the pyschoactive marijuana derived cannabinoid, binds to the CB1 receptor in the brain and to the CB2 receptor in the spleen. Compounds which stimulate the CB1 receptor have been shown to induce analgesia and sedation, to cause mood elevation, to control nausea and appetite and to lower intraocular pressure (Mechoulam, *Cannabinoids as Therapeutic Agents*, CRC Press, Boca Raton, FL (1986), Fride and Mechoulam, *Eur. J. Pharmacol. 231*:313 (1993), Crawley *et al.*, *Pharmacol. Biochem. Behav. 46*:967 (1993) and Smith *et al.*, *J. Pharm. Exp. Therap. 270*:219 (1994)). Compounds which stimulate the CB2 receptor have been shown to suppress the immune system (Mechoulam, *Cannabinoids as Therapeutic Agents*, CRC Press, Boca Raton, FL (1986), Fride and Mechoulam, *Eur. J. Pharmacol. 231*:313 (1993), Crawley *et al.*, *Pharmacol. Behav. 46*:967 (1993) and Smith *et al.*, *J. Pharm. Exp. Therap. 270*:219 (1994)).

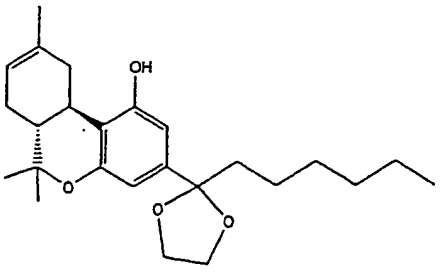
SUMMARY OF THE INVENTION

Disclosed herein is the discovery that cannabinoids with a monocyclic, a fused bicyclic, a bridged bicyclic

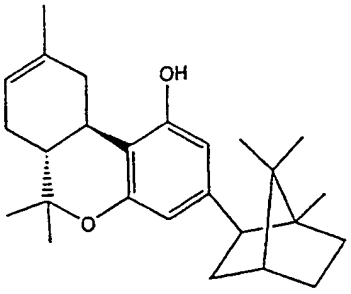
or a bridged tricyclic side chain at the C-3 position show improved binding affinities for the CB1 and/or CB2 receptor compared with known cannabinoids, which typically have a linear side chain at the C-3 position. For example, the cannabinoids AMG3 and AMG14 have a K_i for the CB1 receptor of less than 1.0 nM and AM731 and AM732 have a K_i for the CB2 receptor of less than 10.0 nM (Example 2). In contrast, the K_i of Δ^8-tetrahydrocannabinol for the CB1 and CB2 receptors is only 45 nM and 14 nM, respectively. The structures of these compounds are shown below.



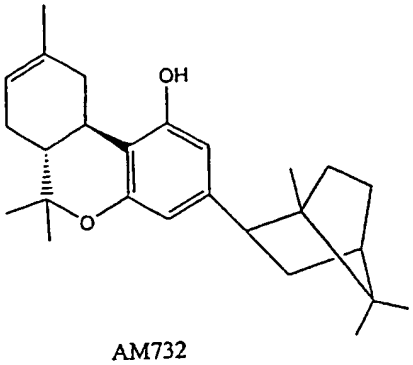
AMG3



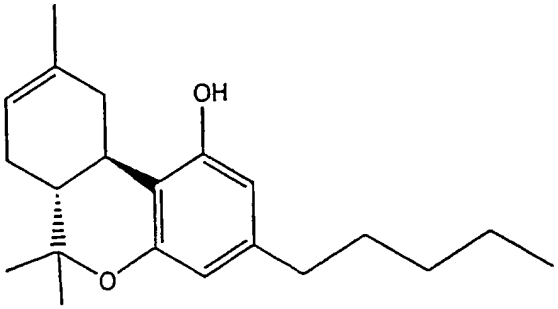
AMG14



AM731



AM732



Delta-8-Tetrahydrocannabinol

Based on these results, novel cannabinoids with increased binding affinity for the CB1 and CB2 receptors are disclosed. Also disclosed are methods of stimulating a CB1 and/or CB2 receptor in a subject.

One embodiment of the present invention is a compound represented by Structural Formula (I):

R-X-Y; (I)

and physiologically acceptable salts thereof.

R is a tricyclic core of a cannabinoid or substituted cannabinoid.

X is covalent bond, -CH- or -CHR_1-, wherein R_1 is a C1 to C3 substituted or unsubstituted alkyl group.

Y is a heterocyclic ring, a substituted heterocyclic ring, a carbocyclic ring, a substituted carbocyclic ring, a fused bicyclic ring system, a substituted fused bicyclic ring system, a bridged bicyclic ring system, a substituted bridged bicyclic ring system, a bridged tricyclic ring system or a substituted bridged tricyclic ring system.

Another embodiment of the present invention is a method of stimulating a CB1 and/or CB2 receptor in a subject. The method comprises administering to the subject a therapeutically effective amount of a compound represented by Structural Formula (I).

The novel compounds of the present invention can be used to stimulate the CB1 or CB2 receptors in a subject at lower doses and higher selectivity than other known CB1 or CB2 receptor agonists. Thus, they are expected to produce fewer side-effects than known CB1 or CB2 receptor agonists when used for treatment, for example, in treating glaucoma, treating autoimmune disease (e.g., lupus erythematosus, rheumatoid arthritis, psoriasis, multiple sclerosis and inflammatory bowel disease such as ulcerative colitis and Crohn's disease), preventing tissue rejection in organ transplant patients, controlling nausea in patients undergoing chemotherapy and enhancing appetite and controlling pain in individuals with AIDS Wasting Syndrome. In addition, some of these compounds are selective agonists for either the CB1 (e.g., AM411) or CB2 receptor (e.g., AM731 and AM732).

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1C shows the structure of a number of examples of novel compounds included in the present invention.

Figures 2A and 2B shows the structure of a number of novel cannabinoid side chains which can be found in the compounds of the present invention.

Figure 3 is a schematic showing a general procedure for the preparation of Δ^8-tetrahydrocannabinol analogs and 2- and 4- substituted deoxy-Δ^8-tetrahydrocannabinols.

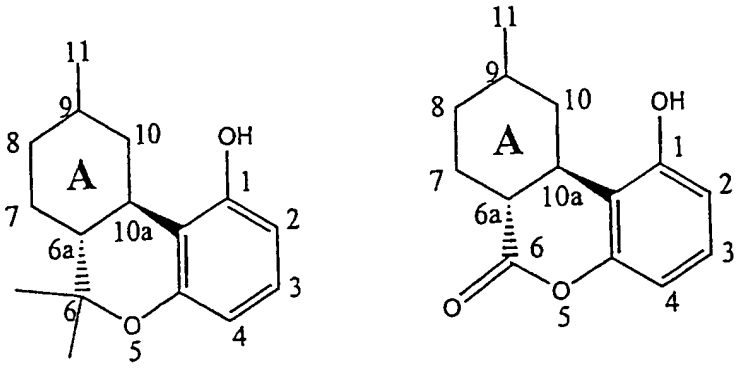
Figure 4 is a schematic of the synthesis of cannabinol analogs with noncyclic side chains.

Figures 5A-5B is a schematic showing the preparation of the rescorinol starting materials used in the syntheses shown in Figures 3 and 4.

DETAILED DESCRIPTION OF THE INVENTION

Cannabinoids have a core tricyclic ring system in which a monohydroxylated phenyl ring and a six membered ring are each fused to a central pyran ring or to a central six-membered lactone ring (preferably to a pyran ring). In addition, cannabinoids are able to induce characteristic physiological effects in mammals, including euphoria, delerium, drowsiness, halluncinations, weakness and/or hyporeflexia. The tricyclic core ring system of many cannabinoids is shown in Structural Formula (II). Other cannabinoids have the tricyclic core shown in Structural Formula (II), modified to include one or more double bonds in Ring A, for example, a double bond between carbons 8 and 9, between carbons 9 and 10 or between carbons 9 and 11. Yet other cannabinoids have the core structures

described above, modified so that the methyl group bonded to carbon 11 has been replaced, for example, with a hydrogen, hydroxyl, hydroxymethyl, halogen (e.g., chloro, bromo, iodo and fluoro), methoxy, ethoxy, nitrile, nitro, halogenated methyl, halogenated ethyl, methoxymethyl, ethoxymethyl, nitromethyl, ethyl or $-CH_2CN$ group. In other cannabinoids, the hydroxyl group at position 1 of the core structure is replaced with -H, $-OCH_3$, $-NH_2$ or $-NHCH_3$. The term "cannabinoid", as it is used herein, also refers to other compounds which: 1) induce one or more of the physiological effects described above which are characteristic of the cannabinoids and 2) have core structures which are related to Structural Formula (II). Also shown in Structural Formula (II) is a numbering system for the atoms in the core tricylic structure.



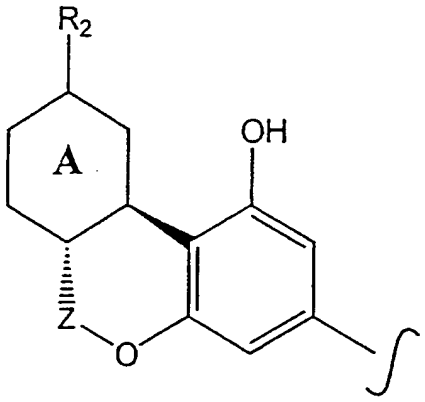
(II)

Cannabinoids also generally have a linear alkyl side chain at position C-3 of the cannabinoid core. In the cannabinoids of the present invention, the linear alkyl side chain is replaced with a heterocyclic ring, a

substituted heterocyclic ring, a carbocyclic ring, a substituted carbocyclic ring, a fused bicyclic ring system, a substituted fused bicyclic ring system, a bridged bicyclic ring system, a substituted bridged bicyclic ring system, a bridged tricyclic ring system or a substituted bridged tricyclic ring system.

Suitable substituents for a cannabinoid include groups which do not significantly diminish the ability of a cannabinoid to activate a cannabinoid receptor. Substitutions can occur at positions 2, 4, 6a-10a or at the three methyl groups. Substitutions at more than one position are possible. Substituents which do no significantly diminish the biological activity of cannabinoids are generally small, pharmacophoric groups. Examples include -H, -OH, $-OCH_3$, $-OCH_2CH_3$, halogen (e.g., chloro, bromo, iodo and fluoro), -CN, azido, isocyanate, isothiocyanate, $-NO_2$, $-CH_3$, $-C(halogen)_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2(halogen)$, $-CH_2CN$, $-CH_2NO_2$, $-CH_2CH_3$, $-CH_2C(halogen)_3$, $-CH_2NH_2$, $-CH_2NHCH_3$ or $-CH_2N(CH_3)_2$. Suitable substituents can be identified by testing modified cannabinoids in the *in vitro* CB1 or CB2 assays described in Example 2. Cannabinoids with other substituents can be prepared by modification of the synthetic procedures described in Example 1, e.g., by replacing alcohol (A) in the synthesis shown in Figure 3 or by replacing the ester/ketone starting material in Figure 4 with suitably substituted analogs.

Preferably, the tricyclic cannabinoid core is represented by Structural Formula (III):



(III)

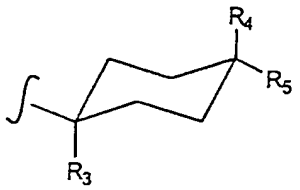
Ring A has from zero to three endocyclic double bonds. Examples include wherein Ring A is completely saturated, wherein Ring A has three double bonds and wherein Ring A has one endocyclic double bond which connects carbons 9 and 10 or 9 and 11. Preferably, Ring A has one endocyclic double bond wich connects carbons 8 and 9. As used herein, a double bond between two ring atoms is an "endocyclic" double bond.

Z is $>C(CH_3)_2$ or -C=O. Z is preferably $>C(CH_3)_2$.

R_2 is -H, -OH, $-OCH_3$, $-OCH_2CH_3$, halogen (e.g., chloro, bromo, iodo and fluoro), $-CN$, $-NO_2$, $-CH_3$, $-C(halogen)_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2(halogen)$, $-CH_2CN$, $-CH_2NO_2$, $-CH_2CH_3$, $-CH_2C(halogen)_3$, $-CH_2NH_2$, $-CH_2NHCH_3$ or $-CH_2N(CH_3)_2$. Preferably, R_2 is $-CH_3$ or $-CH_2OH$.

When the tricyclic cannabinoid core is represented by Structural Formula (III), X and Y, taken together, are a C5-C7 carbocyclic ring, a substituted C5-C7 carbocyclic ring, a C5-C7 heterocyclic ring or a C5-C7 substituted heterocyclic ring.

Carbocyclic rings are non-aromatic rings which have only carbon as the ring atoms. Preferably, carbocyclic rings include from about five to about seven ring carbons and are substituted or unsubstituted. Examples include substituted and unsubstituted cyclopentane, cyclopentene, cyclohexane, cyclohexene, cycloheptane and cycloheptene. A preferred example is a substituted cyclohexane shown below in Structural Formula (IV):

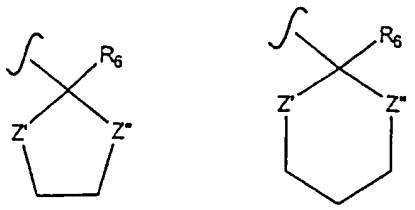


(IV)

R_3 is -H or $-CH_3$.

R_4 and R_5 are independently -H, a C1-C8 straight chained alkyl group or a C1-C8 substituted straight chained alkyl group. Preferably, at least one of R_4 and R_5 is -H.

Heterocyclic rings are non-aromatic rings with carbon and one or more heteroatoms such oxygen, nitrogen and/or sulfur as ring atoms. Preferably, heterocyclic rings contain from about five to about seven ring atoms and are substituted or unsubstituted. Preferred examples of heterocyclic rings are shown below in Structural Formulas (V) and (VI):



(V) (VI)

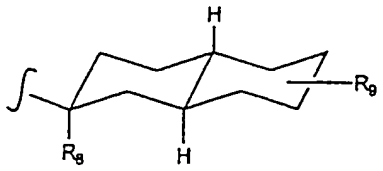
Z′ and Z″ are independently -S-, -O-, -S(O)- or -N(R_7)-. Preferably, Z′ and Z″ are each -O- or -S-.

R_6 is a C1 to about C12 straight chained alkyl or substituted alkyl group. Preferably, R_6 is a C4 to C10 alkyl group.

R_7 is -H or -CH_3.

Other examples of hetetocyclic rings include substituted and unsubstituted 1,3-dioxane, 1,4-dioxane, 1,3-dithiane, 1,4-dithiane, diazetane, tetrahydrofuran, tetrahyrothiophene, morpholine, thiomorpholine, pyrrolidine, piperazine, piperidine and thiazolidine.

A fused bicyclic ring comprises two rings which share two ring atoms. Examples include systems such as decalin and tetralin. A preferred example of a fused bicyclic ring system is represented by Structural Formula (VII):

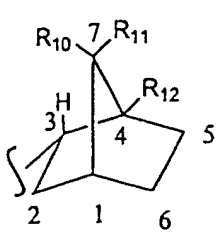


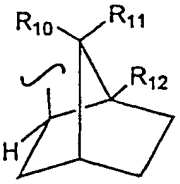
(VII)

R_8 is -H or -CH_3; and

R_9 is -H, a C1-C4 alkyl group or a C1-C4 substituted or unsubstituted alkyl group.

A "bridged bicyclic ring" has two rings in which more than two ring atoms are shared by the two rings. Optionally, a bicyclic ring can have one or more ring heteroatoms such as oxygen, sulfur or nitrogen. A preferred bridged bicyclic ring is a substituted or unsubstituted 2.2.1 seven membered system also referred to as a "norbornyl group". Examples of norbornyl groups are represented by Structural Formula (VIII) and (IX);

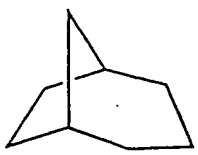




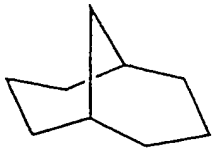
(VIII) (IX)

R_{10}-R_{12} are independently -H, C1-C3 alkyl group or C1-C3 substituted alkyl group. Preferably, R_{10}-R_{12} are independently -H or $-CH_3$.

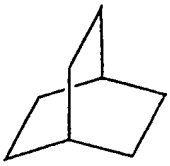
Other examples of suitable bridged bicyclic structures include a 3.2.1 eight-membered bicyclic structure, a 3.3.1 nine-membered bicyclic structure and a 2.2.2 eight-membered structure and a 3.3.2 nine-membered structure. The structures of a 3.2.1 eight-membered bicyclic system, a 3.3.1 nine-membered bicyclic system, a 2.2.2 eight-membered bicyclic system and a 3.3.2 nine-membered bicyclic system are provided by Structural Formulas (X)-(XIII):



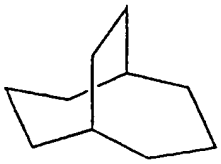
(X)



(XI)



(XII)



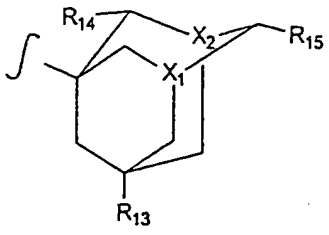
(XIII)

In one example, the bridged bicyclic structures represented by Structural Formulas (X)-(XIII) are substituted by one or more methyl groups.

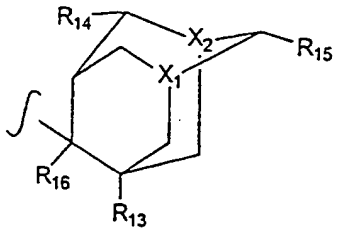
The nomenclature for bridged bicyclic and tricyclic ring systems indicates the number of ring atoms between bridgeheads. A "bridgehead" is an atom shared by both rings. For example, bicyclo 2.2.1. heptane, shown in Structural Formula (VIII), has two (C-2 and C-3), two (C-5 and C-6) and one (C-7) carbons between the bridgeheads (C-1 and C-4). The numbering scheme for the ring atoms in 2.2.1 heptane is also shown in Structural Formula (VIII).

Bridged tricyclic ring systems comprise three rings, each of which shares two or more ring atoms with each of the other two rings. Optionally, a bridged tricyclic ring can have one or more heteroatoms such as oxygen, nitrogen or sulfur. A preferred example is a substituted or unsubstituted 1,1,1,1,1,1-tricyclic ten-

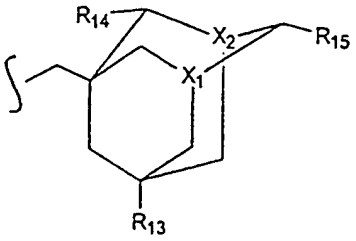
membered ring system, also referred to as an "adamantyl" group. Examples of adamantyl groups are represented by Structural Formula (XIV)-(XVII):



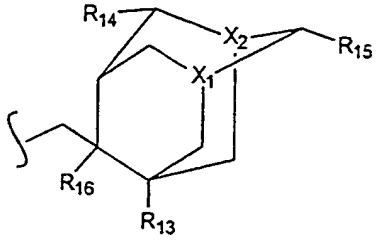
(XIV)



(XV)



(XVI)



(XVII)

R_{13}, R_{14}, R_{15} and R_{16} are independently -H, a C1-C3 alkyl group or a C1 to C3 substituted alkyl group. Preferably, R_{13} is $-CH_3$.

X_1 and X_2 independently are >N- or >CH-. Preferably, X_1 and X_2 are >CH-.

In another preferred embodiment, the novel cannabinoid analogs of the present invention are represented by Formula (III), modified so that the hydroxyl group attached to the phenyl ring is replaced with an -H and/or modified so that the side chain is

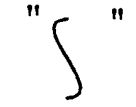
attached to position four of the tricyclic cannabinoid core.

Another example of suitable bridged tricyclic system is a substituted or unsubstituted 0,1,1,1,1,1-tricyclic nine-membered ring system.

Suitable substituents for a carbocyclic ring, a heterocyclic ring, a fused bicyclic ring, a bridged bicyclic ring and a bridged tricyclic ring are generally C1-C8 alkyl groups, substituted C1-C8 alkyl groups and small, pharmacophoric groups. Examples of small, pharmacophoric groups include, but are not limited to, -H, -OH, $-OCH_3$, $-OCH_2CH_3$, halogen (e.g., chloro, bromo, iodo and fluoro), -CN, azido, isocyanate, isothiocyanate, $-NO_2$, $-CH_3$, $-C(halogen)_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2(halogen)$, $-CH_2CN$, $-CH_2NO_2$, $-CH_2CH_3$, $-CH_2C(halogen)_3$, $-CH_2NH_2$, $-CH_2NHCH_3$ or $-CH_2N(CH_3)_2$. Alkyl groups can be straight chained or branched. Suitable substituents for an alkyl group include small, pharmacophoric groups, as described above.

Specific examples of the compounds of the present invention are shown in Figures 1 and 2.

In the structural formulas depicted herein, the single or double bond by which a chemical group or moiety is connected to the remainder of the molecule or compound is indicated by the following symbol:



For example, the corresponding symbol in Structural Formula (VIII) indicates that the norbornyl group, which is represented in Structural Formula (I) by Y, is connected to R or X in Structural Formula (I) by a

single covalent bond with between carbon three of the norbornyl group and R or X.

A "therapeutically effective amount" is the quantity of compound which results in a desired therapeutic effect in a subject, e.g., immune system suppression, decreased nausea in patients undergoing chemotherapy, increased appetite and/or decreased pain in individuals with AIDS Wasting Syndrome or intraocular pressure in individuals with glaucoma. The specific dosage level of active ingredient will depend upon a number of factors, including, for example, biological activity of the particular preparation, age, body weight, sex and general health of the subject being treated. Typically, a "therapeutically effective amount" of the compound ranges from about 10 mg/day to about 1000 mg/day, preferably from about 50 mg/day to about 500 mg/day.

As used herein, a "subject" refers to a human. An "animal" refers to veterinary animals, such as dogs, cats, horses, and the like, and farm animals, such as cows, pigs, guinea pigs and the like.

The compounds of the present invention can be administered by a variety of known methods, including orally, rectally, or by parenteral routes (e.g., intramuscular, intravenous, subcutaneous, nasal or topical). The form in which the compounds are administered will be determined by the route of administration. Such forms include, but are not limited to capsular and tablet formulations (for oral and rectal administration), liquid formulations (for oral, intravenous, intramuscular or subcutaneous administration) and slow releasing microcarriers (for rectal, intramuscular or intravenous administration).

The formulations can also contain a physiologically acceptable vehicle and optional adjuvants, flavorings, colorants and preservatives. Suitable physiologically acceptable vehicles may include saline, sterile water, Ringer's solution, and isotonic sodium chloride solutions.

The compounds of the present invention can be prepared by the syntheses shown in Figures 3-5. Specific conditions for reactions shown in Figures 3-5 are provided in Example 1.

Also included in the present invention are physiologically acceptable salts of the novel compounds disclosed herein. Salts of compounds containing a phenolic group or other acidic functional group can be prepared by reacting with a suitable base, for example, a hydroxide base or amine base. Salts of acidic functional groups contain a countercation such as sodium, potassium, ammonium and the like. Salts of compounds containing an amine or other basic group can be obtained, for example, by reacting with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, perchloric acid and the like. Compounds with quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like.

The novel compounds of the present invention have utilities other than immunomodulation. For example, the disclosed cannabinoids can be used to screen for cells which express cannabinoid receptors (CB1 or CB2). The cells are contacted with a radiolabelled cannabinoid, washed to remove unbound compound and then counted to assess retained radioactivity. Cells which retain radioactivity bind cannabinoids and are there likely to

express a cannabinoid receptor. Preferably, the cannabinoid is a CB1 or CB2 selective cannabinoid and therefore identifies cells which express the CB1 or CB2 receptor, respetively.

The disclosed cannabinoids can also be used to identify other compounds which bind to a cannabinoid receptor. For example, radiolabelled cannabinoids can be used in place of CP-55,940 in the CB1 or CB2 assay described in Example 1. Radiolabeled cannabinoids can be prepared by, for example, by reducing the ketones used in Method II of Figure 5 with a suitable radiolabeled reducing agent such a tritiated sodium borohydride and oxidizing back to the ketone with a suitable oxidizing agent such as pyridinium chloro chromate (PCC). Preferably, the cannabinoid is selective for the CB1 or CB2 receptor.

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1 - Preparation of the compound of the present invention

Resorcinol synthesis

(I). Resorcinols synthesized by method I in Figure 5

A procedure for preparing resorcinols is described in Dominiami, *et al., J. Org. Chem. 42*:344 (1977). The crude resorcinols obtained by this method were purified by silica gel column chromatography eluted with a 2:1 mixture of petroleum ether and acetone.

(II). Resorcinols synthesized by method II

Preparation of 5-Bromo-3,5-Dimethoxy Benzene. 100 mmol of 3,5-dimethoxyaniline were mixed with 75 ml of 48% hydrobromic acid. 150 mmol of sodium nitrite powder were added portionally over 20 minutes with rigorous stirring. The reaction was monitored by iodine-starch test paper until the paper turned blue. The resulting diazonium salt solution was added to a pre-prepared boiling solution of 50 mmol copper (I) bromide in 7 ml of 48% hydrobromic acid. The addition was complete after 20 minutes. The reaction mixture was then heated for 30 minutes with rigorous stirring. Steam distillation of the reaction mixture provided a white solid product with a yield of 40%.

Preparation of 1'-hydroxy-1-alkyl-3,5-dimethoxybenzene. 1 mmol of 3,5-dimethoxyphenylmagnesium bromide was prepared in 8 ml of anhydrous THF according to procedures disclosed in Harvill and Herbst, *J. Org. Chem.*, *9*:21 (1944), the entire teachings of which are incorporated herein by reference. A solution of 1.1 mmol of a suitable ketone in 2 ml of anhydrous THF was added dropwise to the Grignard reagent solution. The mixture was refluxed for 2 to 3 hours and then quenched with the addition of saturated ammonium chloride solution. After work up and purification by column chromatography, product was collected in a yield of 95%.

Preparation of 1-alkyl-3,5-dimethoxybenzene. This compound was synthesized through lithium ammonia reduction of 1'-hydroxy-1-alkyl-3,5-dimethoxybenzene by the method described in Gray *et al.*, *J. Org. Chem.*, *Vol.40*:3151 (1975), the entire teachings of which are incorporated herein by reference.

Preparation of 5-alkyl-resorcinol. This resorcinol was perpetrated by demethylation of 1-alkyl-3,5-dimethoxybenzene through the method described in Dominiami, *et al., J. Org. Chem.* 42:344 (1977), the entire teachings of which are incorporated herein by reference.

(III) Resorcinols synthesized by method III in Figure 5

Preparation of 1-alkyl-3,5-dimethoxybenzene. A ethereal 10 mmol of 3,5-dimethoxybenzylmagnesium bromide was prepared in the usual manner with 40 ml of anhydrous ether according to procedures disclosed in Harvill and Herbst, *J. Org. Chem.*, 9:21 (1944). The solution of Grignard reagent was concentrated to 15 ml and transferred into an Ace pressure tube containing a 10 ml ethereal solution of 10 mmol of a suitable tertiary alkyl bromide. The mixture was sealed and heated in a 100°C oil bath with stirring for 30 minutes, as described in Osama, *et al., J. Org. Chem.*, 36:205 (1971), Ohno, *et al., J. Org. Chem.*, 53:729 (1988) and Love, *et al., J. Med. Chem.*, 16:1200 (1973), the entire teachings of which are incorporated herein by reference. The crude product was purified through column chromatoghraphy with a yield about 25%.

Preparation of 5-alkyl-resorcinol. This resorcinol was prepared by demethylation of 1-alkyl-3,5-dimethoxybenzene by methods described in Dominiami, *et al., J. Org. Chem.*, 42:344 (1977), the entire teachings of which are incorporated herein by reference.

(IV). Resorcinols synthesized by method IV in Figure 5

The procedure for the preparation of these resorcinols is the same as described in (III), except

that the Grignard reagent was prepared using tetrahydrofuran.

(V). Resorcinols synthesized by method V in Figure 5

A mixture of 100 mmol resorcinol and 100 mmol tertiary alcohol in 200 ml of 70% methanesulfonic acid was stirred at 0°C for 12 hours for the preparation of linear side chain resorcinols, and stirred for 3 to 4 hours at room temperature for preparation of cyclic side chain resorcinols. The reaction was quenched by addition of an excess of water. The crude product was purified by column chromatography. The column was eluted with 2:1 mixture of petroleum ether and acetone. Yield was about 70%.

Synthesis of Δ^8-Tetrahydrocannabinol Analogs Via the Method of Scheme 1 of Figure 3.

A mixture of 1 mmol of the resorcinol, 1 mmol trans-p-mentha-2, 8-dien-1-ol and 18 mg of p-toluenesulfonic acid monohydrate in 10 ml of chloroform was stirred and heated in a 70°C oil bath for 2 to 4 hours. Then the reaction temperature was lowered to room temperature and quenched by addition of 5 ml of saturated sodium bicarbonate solution. After separation, the aqueous layer was extracted twice with methylene chloride. The combined organic layer was washed with brine and dried over sodium sulfate. Removal of solvent by vacuum evaporation provides a yellow oil crude product. The product was purified by column chromatography. By eluting with 20:1 mixture of petroleum ether and ethyl acetate. The yield was generally about 65%. For some stereoisomers, HPLC

purification was performed with a chiral column. The mobil phase was a mixture of hexane and isopropanol.

Synthesis of 1-Deoxy-Δ^8-Tetrahydrocannabinol Via the Method of Scheme 2 in Figure 3

A mixture of 1 mmol of the phenol, 3 mmol trans-p-mentha-2, 8-dien-1-01 and 35 mg of p-toluenesulfonic acid monohydrate in 10 ml of chloroform was stirred and heated in a 70°C oil bath for 4 to 8 hours. Then the reaction temperature was lowered to room temperature. The reaction was quenched by addition of 5 ml of saturated sodium bicarbonate solution. After separation, the aqueous layer was extracted twice by methylene chloride. The combined organic layer was washed by brine and dried over sodium sulfate. Removal of solvent by vacuum evaporation provided a yellow oil crude product. The product was purified by column chromatography, eluting with 20:1 mixture of petroleum ether and ethyl acetate. The yield was generally about 15% to 20%.

Synthesis of Cannabinol and 1-Deoxy-Cannabinol Analogs Via the Method of Scheme 3 of Figure 4

The experimental procedures are as described in Love, *et al.*, *J. Med. Chem.*, *16*:1200 (1973), Meltzer, et al., Synthsis, 1981, 985, and Gareau, *et al.*, *Bioorg. Med. Chem. Lett.*, *6*:189 (1996), the entire teachings of which are incorporated herein by reference.

Example 2 - Compounds of the present invention bind to the CB1 and/or CB2 receptor

RADIOLIGAND BINDING ASSAY

The binding affinities of the novel compounds described in this invention for the central cannabinoid receptor was assessed using rat forebrain membranes as a source of CB1. Membranes were prepared as described by the method of Dodd *et al.*, *Brain Res.* *226*:107 (1981), the entire teachings of which are incorporated herein by reference. Rat whole brains minus the cerebral cortex were diced with a razor blade and homogenized in 0.32 M sucrose, pH 7.4. The resulting suspension was spun at 400 x g at 4°C. The supernatant was decanted and layered over 1.2 M sucrose in TME buffer (25 mM Tris base, 5 mM $MgCl_2$ 1 mMEDTA, pH 7.4) and spun at 109,000 x g. The interface containing plasma membrane protein was collected, pooled and layered over 0.8 M sucrose in TME, pH 7.4. The pellet was carefully resuspended in TME, pH 7.4 and the total protein content was assayed by the method of Markwell *et al.*, *Anal. Biochem.* *87*:206 (1978), the entire teachings of which are incorporated herein by reference. Protein was aliquotted, frozen under liquid nitrogen and stored at -80°C until use.

Approximately 30μg of tissue was incubated in silanized 96 well microtiter plate with TME containing 0.1% essentially fatty acid free bovine serum albumin (BSA), 0.8 nM [H^3]CP-55,940 and various concentrations of the test compound in a final volume of 200 μL. Assays were incubated at 30°C for 1 hour. The samples were filtered using Packard Filtermate 196 and Whatman GF/C Filterplates and washed with wash buffer (TME)

containing 0.5% BSA. Radioactivity was detected using MicroScint 20 scintillation cocktail added directly to the dried filterplates, and the filterplates were counted using a Packard Instruments Top-Count. Nonspecific binding was assessed using 100 nM CP-55,940. Data collected from three independent experiments performed with duplicate determinations were normalized between 100% and 0% specific binding for [H^3]CP-55,940, determined using buffer and 100 nM CP-55,940. The normalized data was analyzed using a 4 parameter nonlinear logistic equation to yield IC_{50} values. Data from at least two independent experiments performed in duplicate were used to calculate IC_{50} values which were convered to K_i values using the assumptions of Cheng and Prusoff, *Biochem. Pharmacol.*, *22*:3099 (1973), the entire teachings of which are incorporated herein by reference.

Mouse spleen was used a source of CB2 receptors to assess binding affinity of analogs described in this invention. The CB2 binding assay was conducted in the same manner as for CB1. Silanized centrifuge tubes were used throughout to minimize receptor loss due to adsorption.

The K_is (nanomolar) for a number of the compounds of the present invention are shown in the Table below:

Table

Compound	K_i in nM for the CB1 Receptor	K_i in nM for the CB2 Receptor
AM405	19.1	
AM406	14.5	
AM410	25.8	22.3
AM409	75.3	
AM407	9.1	
AM408	18.3	
AM412	182.9	85.0
AMG3	0.32	1.7
AMG9	3.6	
AMG14	0.2	
AM411	6.9	52.0
AM722	78.2	40.3
AM729	29.3	26.9
AM723	382.6	2845.0
AM728	30.7	32.8
AM731	60.6	6.1
AM732	20.1	2.0

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

CLAIMS

What is claimed is:

1. A compound represented by the following structural formula:

R-X-Y;

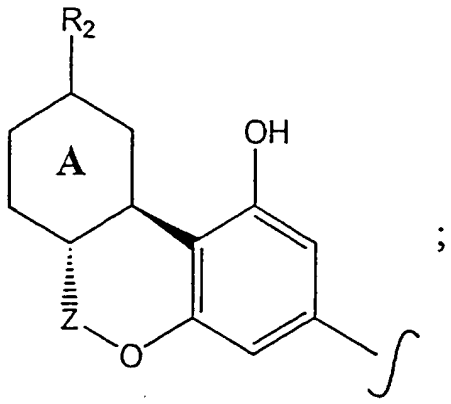
and physiologically acceptable salts thereof, wherein:

R is a tricyclic core of a cannabinoid or substituted cannabinoid;

X is a covalent bond, -CH- or -CHR_1-, wherein R_1 a C1 to C3 substituted or unsubstituted alkyl group; and

Y is a heterocyclic ring, a substituted heterocyclic ring, a carbocyclic ring, a substituted carbocyclic ring, a fused bicyclic ring system, a substituted fused bicyclic ring system, a bridged bicyclic ring system, a substituted bridged bicyclic ring system, a bridged tricyclic ring system or a substituted bridged tricyclic ring system.

2. The compound of Claim 1 wherein R is represented by the following structural formula:



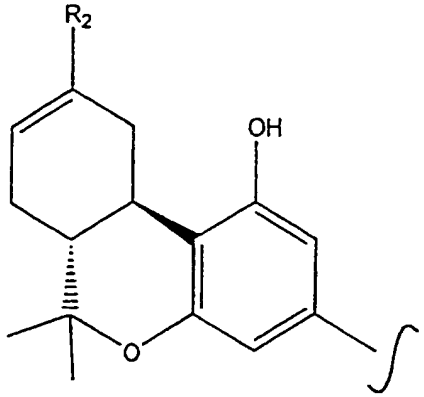
;

wherein Ring A has zero to three endocyclic double bonds;

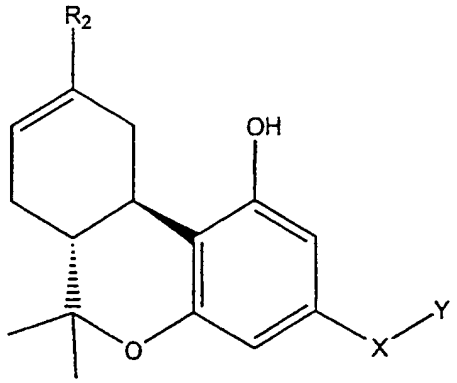
Z is $>C(CH_3)_2$ or -C=O; and

R_2 is -H, -OH, $-OCH_3$, $-OCH_2CH_3$, halogen, -CN, $-NO_2$, $-CH_3$, $-C(halogen)_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2(halogen)$, $-CH_2CN$, $-CH_2NO_2$, $-CH_2CH_3$ or $-CH_2C(halogen)_3$, $-CH_2NH_2$, $-CH_2NHCH_3$ or $-CH_2N(CH_3)_2$.

3. The compound of Claim 2 wherein R is represented by the following structural formula:



;



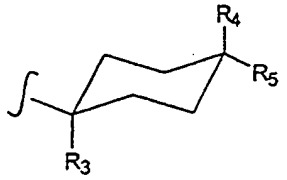
;

wherein R_2 is $-CH_3$ or $-CH_2OH$.

4. The compound of Claim 3 wherein the compound is represented by the following structural formula:

wherein X is a covalent bond and Y is a C5-C7 carbocyclic ring, a substituted C5-C7 carbocyclic ring, a C5-C7 heterocyclic ring or a C5-C7 substituted heterocyclic ring.

5. The compound of Claim 4 wherein X is represented by the following structural formula:



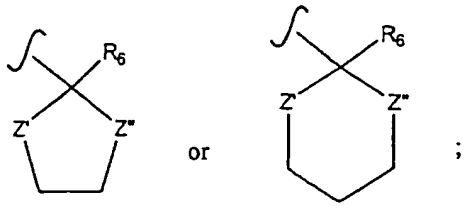
;

wherein:

R_3 is -H or $-CH_3$;

R_4 and R_5 are independently -H or a C1 to C8 substituted or unsubstituted straight chained alkyl group and wherein at least one of R_4 and R_5 is -H.

6. The compound of Claim 4 wherein X is a covalent bond and Y is represented by a structural formula selected from:



;

wherein:

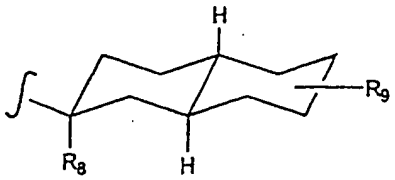
Z' and Z" are independently -S-, -O- or -N(R_7)-;

R_6 is a substituted or unsubstituted C1 to about C12 straight chained alkyl group; and

R_7 is -H or -CH_3.

7. The compound of Claim 6 wherein Z' and Z" are each -O- or -S- and R_6 is a C4 to C10 alkyl group.

8. The compound of Claim 4 wherein X is a covalent bond and Y is represented by the following structural formula:



;

wherein:

R_8 is -H or -CH_3; and

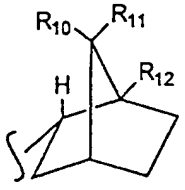
R_9 is -H, a substituted or unsubstituted C1-C4 alkyl group.

9. The compound of Claim 3 wherein X is a covalent bond and Y is a bridged bicyclic ring system, a substituted bridged bicyclic ring system, a bridged tricyclic ring system or a substituted bridged tricyclic ring system.

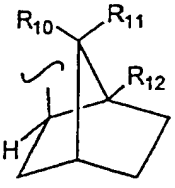
10. The compound of Claim 9 wherein Y is a substituted or unsubstituted 0,1,1,1,1,1-tricyclic nine-membered ring system, 1,3,3-bicyclic nine-membered ring system, 1,2,3-bicyclic eight-membered ring system, 1,1,1,1,1,1-tricyclic ten-membered ring system, 1,1,3-bicyclic nine-membered ring system or 1,3-bicyclic six-membered ring system.

11. The compound of Claim 3 wherein the X is a covalent bond and Y is a substituted or unsubstituted norbornyl ring system.

12. The compound of Claim 11 wherein the norbornyl ring system is represented by the following structural formula:



or



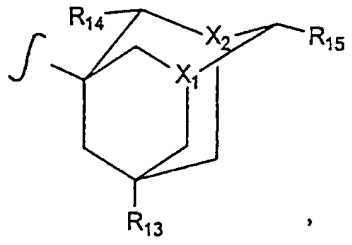
;

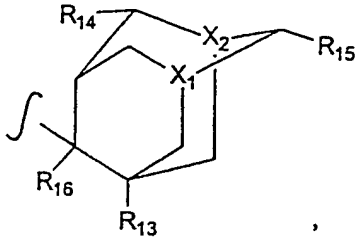
wherein R_{10}-R_{12} are independently -H, C1-C3 alkyl group or C1-C3 substituted alkyl group.

13. The compound of Claim 12 wherein R_{10}-R_{12} are independently -H or -CH_3.

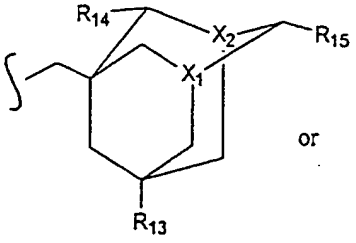
14. The compound of Claim 3 wherein X is a covalent bond and Y is a substituted or unsubstituted adamantyl ring system which contains zero, one or two heteroatoms.

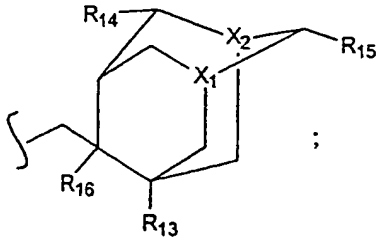
15. The compound of Claim 14 wherein Y is represented by the structural formula:



,


,



or


;

wherein:

R_{13}, R_{14}, R_{15} and R_{16} are independently -H, C1-C3 alkyl group or C1 to C3 substituted alkyl group; and

X_1 and X_2 independently are >N- or >CH-.

16. The compound of Claim 15 wherein R_{14}-R_{16} are each -H, R_{13} is $-CH_3$ and X_1 and X_2 are >CH-.

17. A method of stimulating a CB1 or CB2 receptor in a subject, comprising administering to the subject a therapeutically effective amount of a compound represented by the following structural formula:

R-X-Y;

and physiologically acceptable salts thereof;

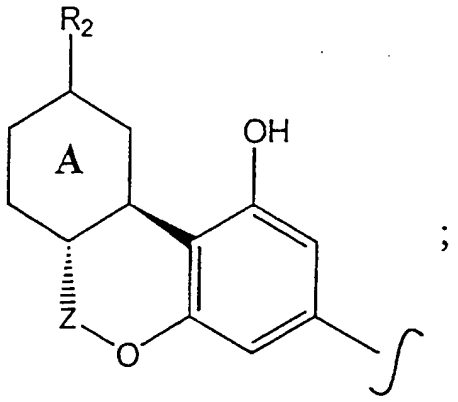
wherein:

R is a tricyclic core of a cannabinoid or substituted cannabinoid;

X is a covalent bond, $-CH_2-$ or $-CHR_1-$, wherein R_1 a C1 to C3 substituted or unsubstituted lower alkyl group; and

Y is a heterocyclic ring, a substituted heterocyclic ring, a carbocyclic ring, a substituted carbocyclic ring, a fused bicyclic ring system, a substituted fused bicyclic ring system, a bridged bicyclic ring system, a substituted bridged bicyclic ring system, a bridged tricyclic ring system or a substituted bridged tricyclic ring system.

18. The method of Claim 17 wherein R is represented by the following structural formula:



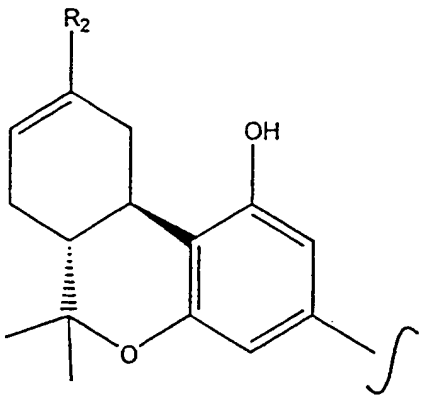
;

wherein Ring A has zero to three endocyclic double bonds;

Z is $>C(CH_3)_2$ or -C=O; and

R_2 is -H, -OH, $-OCH_3$, $-OCH_2CH_3$, halogen, -CN, $-NO_2$, $-CH_3$, $-C(halogen)_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2(halogen)$, $-CH_2CN$, $-CH_2NO_2$, $-CH_2CH_3$, CH_2NH_2, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$ or $-CH_2C(halogen)_3$.

19. The method of Claim 17 wherein R is represented by the following structural formula:

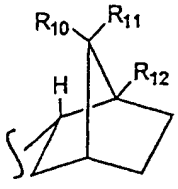


;

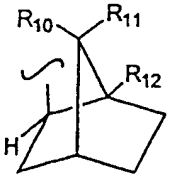
wherein R_2 is $-CH_3$ or $-CH_2OH$.

20. The method of Claim 19 wherein X is a covalent bond and Y is a substituted or unsubstituted norbornyl ring system.

21. The method of Claim 20 wherein the norbornyl ring system is represented by the following structural formula:



or

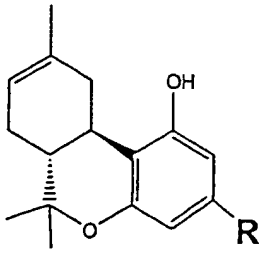


;

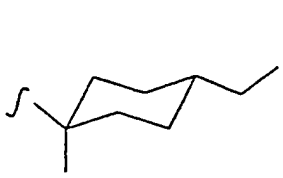
wherein R_{10}-R_{12} are independently -H, C1-C3 alkyl or C1-C3 substituted alkyl.

22. The method of Claim 21 wherein R_{10}-R_{12} are independently -H or $-CH_3$.

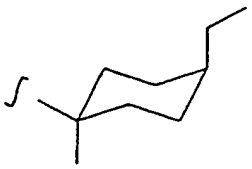
23. A substituted or unsubstituted cannabinoid having substituted at C-3 with a heterocyclic ring, a substituted heterocyclic ring, a carbocyclic ring, a substituted carbocyclic ring, a fused bicyclic ring, a substituted fused bicyclic ring, a bridged bicyclic ring, a substituted bridged bicyclic ring, a bridged tricyclic ring or a substituted bridged tricyclic ring, and physiologically acceptable salts thereof.



R =

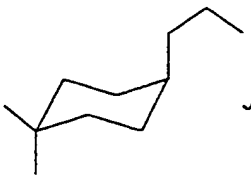


AM405

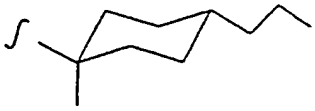


AM406

AM410



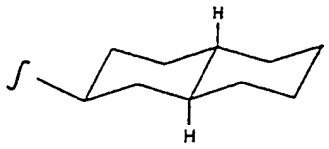
AM409



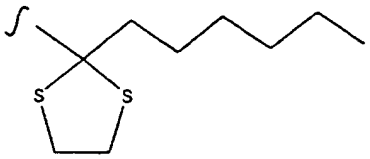
AM407

AM408

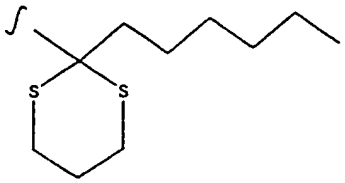
FIGURE 1A



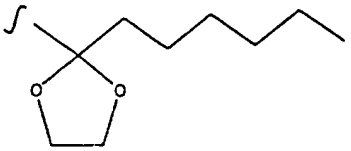
AM412



AMG3



AMG9



AMG14

FIGURE 1B

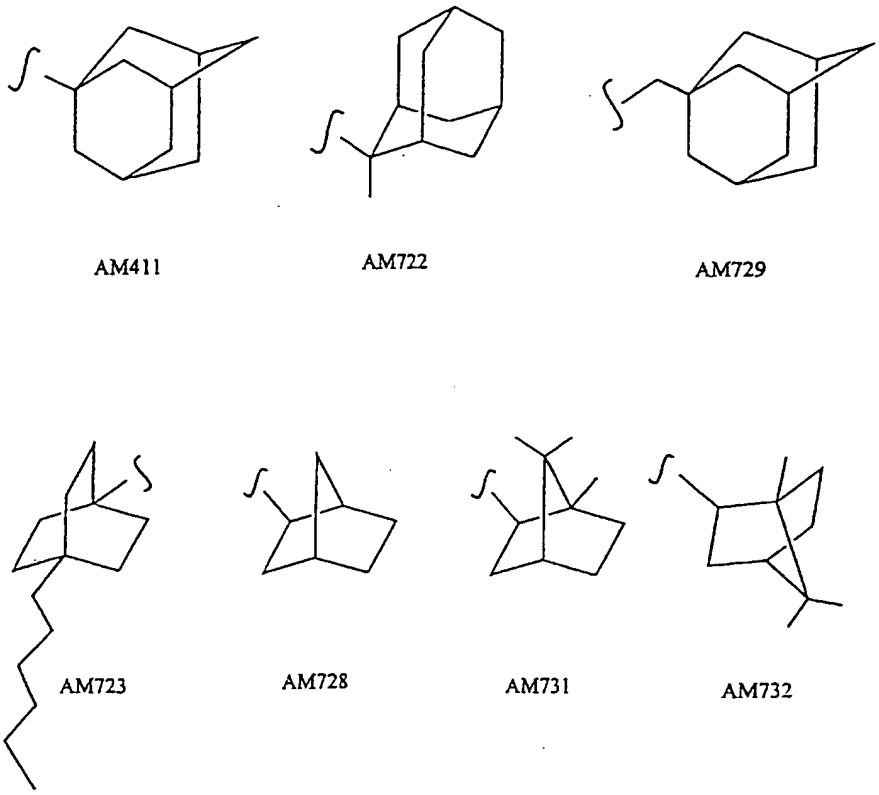


FIGURE 1C

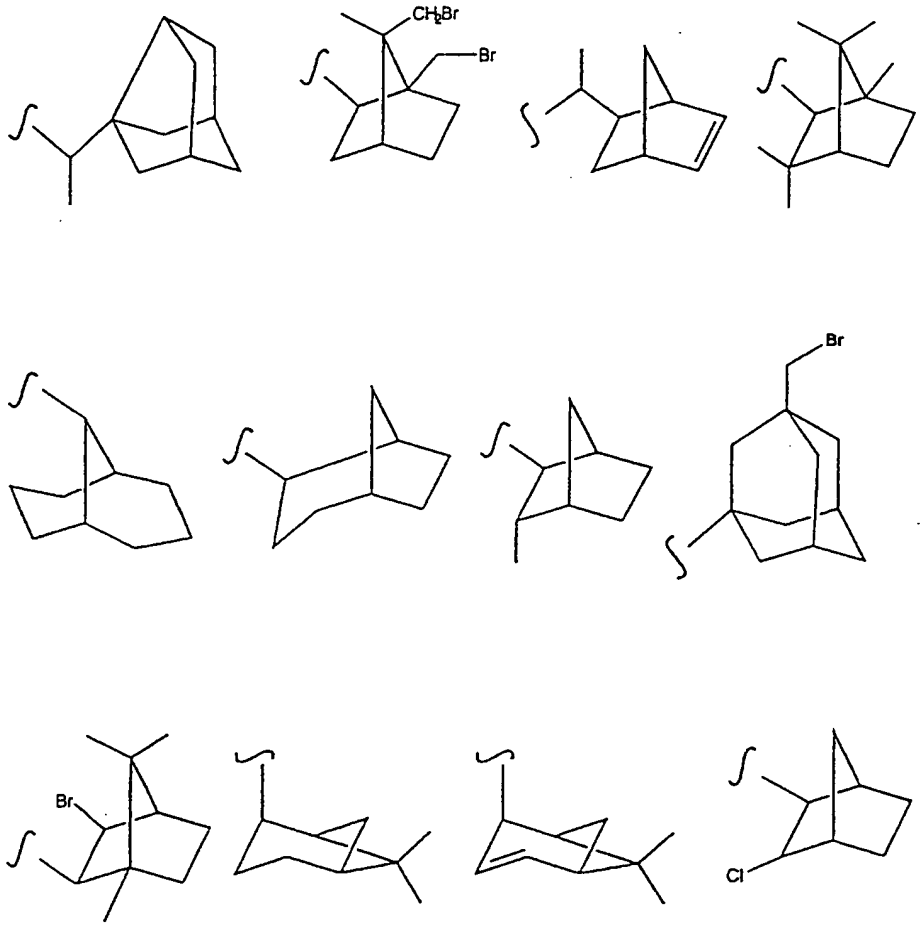


FIGURE 2A

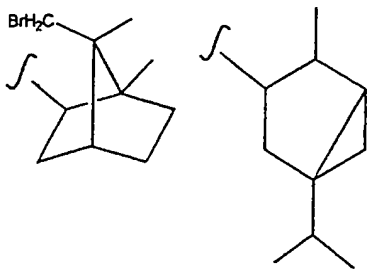
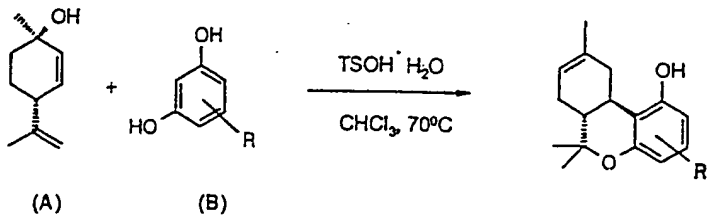


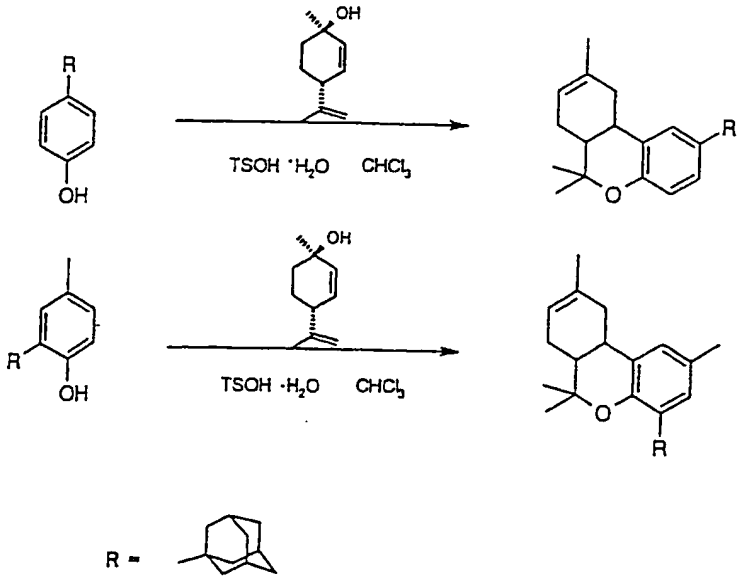
FIGURE 2B

SCHEME 1



(A) (B)

SCHEME 2.



R =

FIGURE 3

Scheme 3.

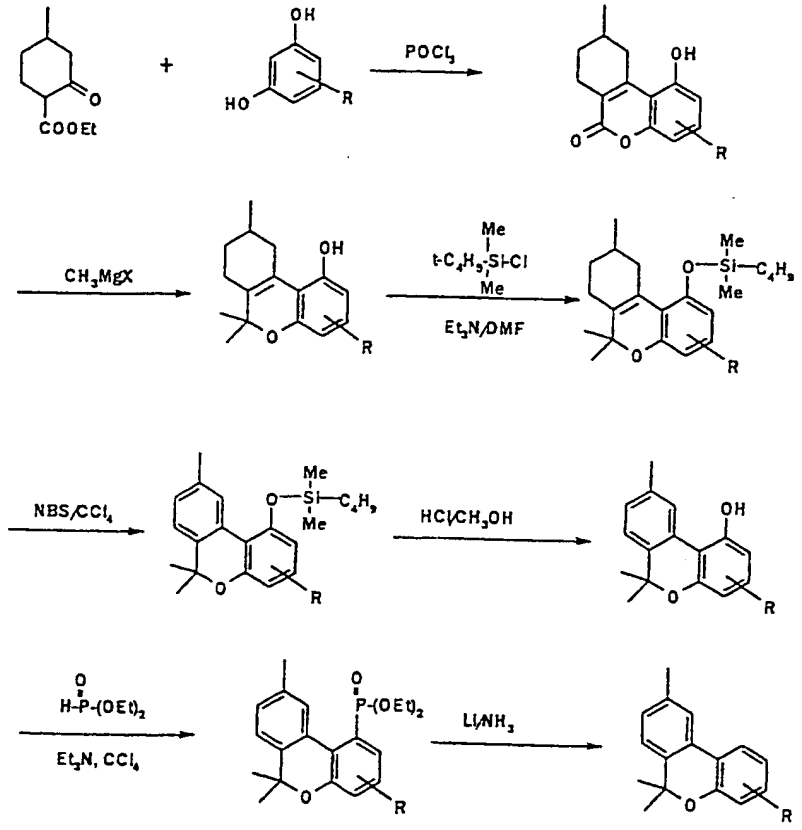
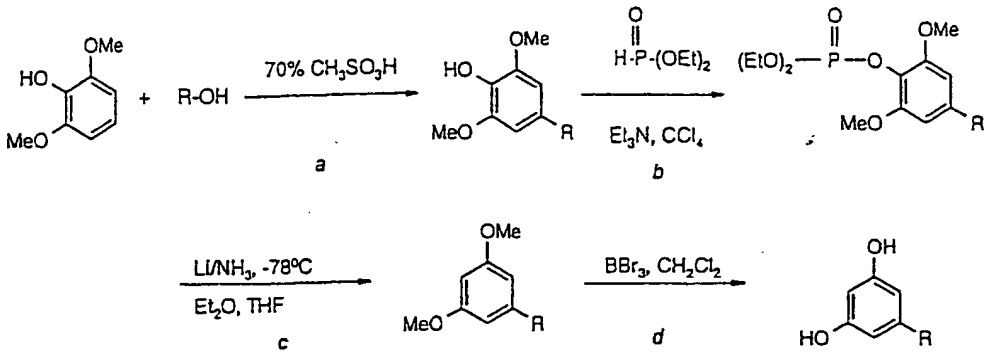


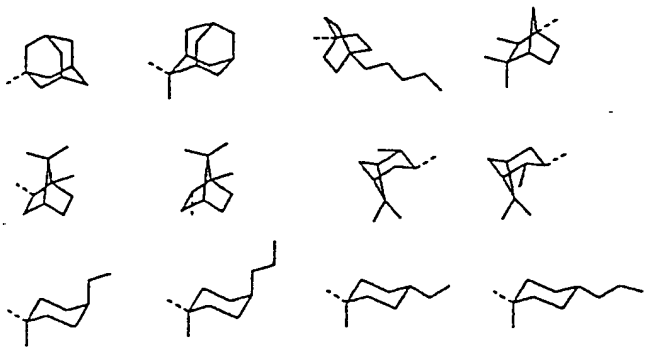
FIGURE 4

Method I:

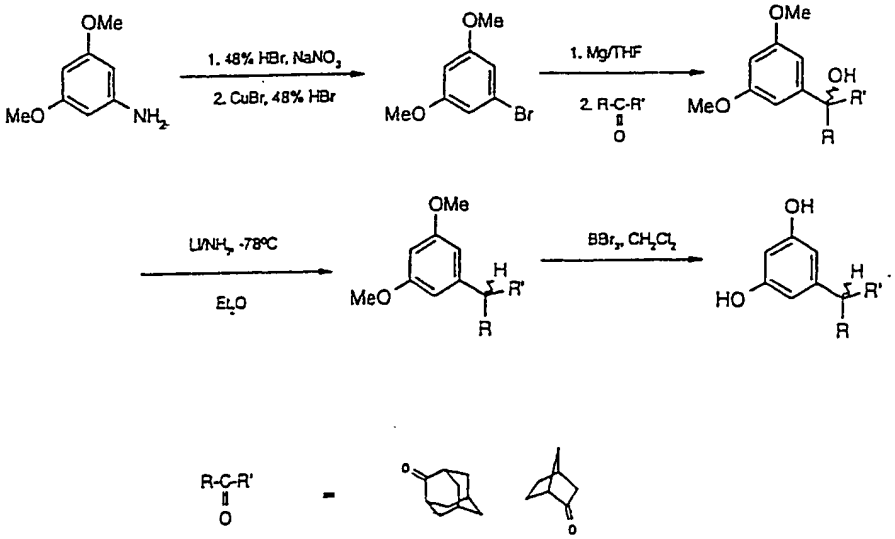


ROH is tertiary or secondary alcohols

R =



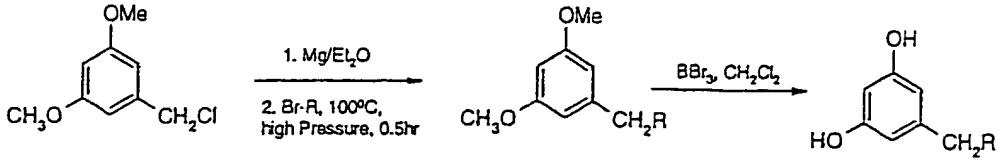
Method II:



R-C-R' =

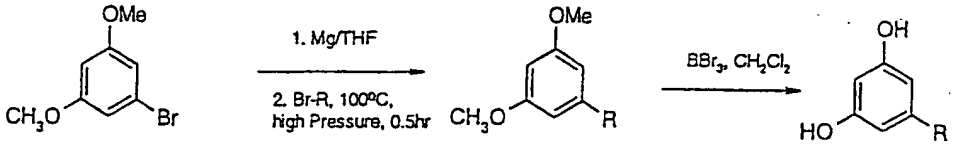
FIGURE 5A

Method III:



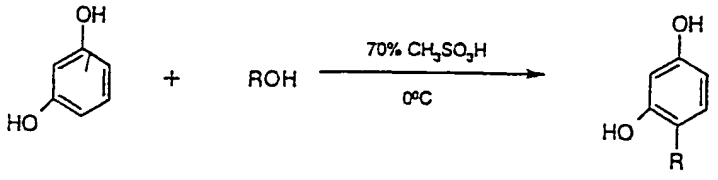
R =

Method IV:



R =

Method V:



ROH is tertiary alcohol

R =

FIGURE 5B